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Journal of Neuroimmunology 83 (1998) 148–156

Journal of
Neuroimmunology

Immunomodulatory effects of cigarette smoke

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Received 7 March 1997; received in revised form 20 October 1997; accepted 24 October 1997

Abstract

Cigarette smoke is a major health risk factor which significantly increases the incidence of diseases including lung cancer and respiratory infections. This increased susceptibility may result from cigarette smoke-induced impairment of the immune system. While the acute effects of cigarette smoke on the immune system are less clear, chronic exposure to cigarette smoke or nicotine causes T cell unresponsiveness. This apparent T cell anergy may account for or contribute to the immunosuppressive and anti-inflammatory properties of cigarette smoke/nicotine. Nicotine-induced immunosuppression may result from its direct effects on lymphocytes, indirectly through its effects on the neuroendocrine system, or both. © 1998 Elsevier Science B.V.

Keywords: Cigarette smoke; Nicotine; Immune response; Inflammation; Neuroimmune modulation

1. Introduction

Tobacco smoke is a complex mixture of thousands of different chemicals many of which have toxic and/or carcinogenic activity (Stedman, 1968; Hoffmann et al., 1979). The constituents of mainstream tobacco smoke (smoke drawn into the mouth during puffs) are principally encountered by smokers; environmental tobacco smoke (smoke originating mostly from the smoldering end of a cigarette between puffs and exhaled mainstream tobacco smoke) is responsible for involuntary or 'passive' smoking by non-smokers (US Department of Health and Human Services, 1993).

Bioassays using tobacco smoke have shown that the majority of genotoxic and carcinogenic substances as well as nicotine are present in the particulate phase (material from cigarette smoke retained by the Cambridge filter comprised mostly of particles > 0.1 μm diameter) of mainstream cigarette smoke (Dube and Green, 1982). The vapor phase (substances that pass through the Cambridge filter), has several known carcinogens, but has not been shown to be tumorigenic in inhalation assays (Hoffmann and Wynder, 1986).

Interest in understanding the mechanism of action by which cigarette smoke/nicotine influences the immune system stems from the recognition that tobacco smoking is a major cause of mortality and morbidity, responsible for over 400,000 deaths yr^{-1} in the United States; the direct health care costs related to cigarette smoking exceed US$50 billion yr^{-1} (US Department of Health and Human Services, 1994). Tobacco smoke has been demonstrated to significantly increase the incidence of heart disease, cancer at various sites, in particular the lung, and susceptibility to respiratory diseases (US Department of Health, Education and Welfare, 1979). Moreover, some recent data suggest that smoking may be a risk factor in faster development of AIDS in HIV-1-seropositive individuals, higher susceptibility of AIDS patients to develop *Pneumocytis carinii* infections, and higher frequency of transmission of AIDS from smoking mothers to their offspring (Burns et al., 1991; Nieman et al., 1993; Burns et al., 1994).

In recent years, there has been growing concern that non-smokers may also be at risk for some of the cigarette smoke-associated diseases as a result of involuntary exposure to environmental tobacco smoke. Despite quantitative differences, the chemical composition of environmental tobacco smoke is very similar to mainstream tobacco smoke and may predispose people to lung cancer and increased risks for lower respiratory tract infections (US Department of Health and Human Services, 1993).

Increased susceptibility of smokers to respiratory tract diseases and cancer may reflect cigarette smoke-induced impairment of the immune system (Holt and Keast, 1977).

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It has recently been postulated that atherosclerosis, which is significantly more prevalent in smokers, may also be an immunologically mediated disease (Wick et al., 1995). Thus, most of the deleterious effects of tobacco smoke on human health may reflect the adverse effects of tobacco smoke on the immune system. Immunosuppressive properties of cigarette smoke have been well established in a variety of experimental animal models and humans (Johnson et al., 1990; Sopori et al., 1994). However, the manner in which cigarette smoke affects the immune system is not clearly understood. There is increasing evidence that nicotine, a major component in cigarette smoke, may significantly contribute to cigarette smoke-induced immunosuppression (Sopori et al., 1993). This review will mainly focus on the effects of various components of cigarette smoke on the immune system and potential mechanisms through which cigarette smoke may affect the immune response.

2. Effects of cigarette smoke on the human immune system

The possibility that human diseases associated with cigarette smoke reflect the effects of tobacco smoke on the immune system was recognized in the 1960s (reviewed in Holt and Keast, 1977). Since then, a large body of evidence tends to support this inference (Holt, 1987; Johnson et al., 1990; Sopori et al., 1994). Human smokers are more likely to develop influenza and have lower antibody titers to influenza virus (Finklea et al., 1969; Aronson et al., 1982; Kark et al., 1982). Prenatal and postnatal exposures to environmental tobacco smoke have been linked to enhanced susceptibility of children to respiratory infections and development of asthma (US Department of Health and Human Services, 1993). In humans, effects of cigarette smoke on the immune system may depend on the amount and duration of smoke exposure, ethnic background, and the sex of the smoker (reviewed in Sopori et al., 1994). Effects of cigarette smoke on the human immune system are summarized in the following.

Most studies investigating the effects of tobacco smoke on lymphocytes have reported a leukocytosis (Corre et al., 1971) with increased numbers of all lymphocyte populations (Hughes et al., 1985). Both CD4 and CD8 T cell subpopulations may increase in smokers (Smart et al., 1986), however, increases in these populations and changes in CD4/CD8 ratios may be modified by the dose and duration of smoke exposure and the ethnic background of the smoker (Tollerud et al., 1991). Similarly, increases in B cell numbers as the result of cigarette smoking have been reported (Hughes et al., 1985; Smart et al., 1986).

The relationship between cigarette smoking and the effects on in vitro lymphocyte functions in human smokers is debatable. Some groups have reported significant decreases in the proliferative response of lymphocytes to T cell mitogens, while others report no significant differences between smokers and non-smokers in this response (reviewed in Sopori et al., 1994). Decreases in NK cell activity in smokers have been reported by several laboratories (Ferson et al., 1979; Tollerud et al., 1989), however, these changes may be affected by the ethnic background of the population studied (Tollerud et al., 1989).

Cigarette smoking has also been shown to decrease the serum levels of most of the immunoglobulin classes (Gerrard et al., 1980; Andersen et al., 1982), excepting IgE which is significantly elevated in smokers (Burrows et al., 1981). Higher serum levels of IgE in smokers is not correlated with increased skin-test reactivity, and smokers exhibit significantly lower skin-test reactivity for a given value of IgE than non-smokers (Burrows et al., 1982). Thus, in spite of higher IgE levels, IgE-mediated responses are weaker in smokers than non-smokers. This may account for the lower incidence of allergic conditions among tobacco smokers (Burrows et al., 1976).

Cigarette smoke is a significant risk factor in respiratory tract illnesses including chronic obstructive lung disease (Haynes et al., 1966; Doll and Peto, 1976). The bronchoalveolar lavage from cigarette smokers has increased numbers of alveolar macrophages (AMs) and neutrophils (Adesina et al., 1991; Bosken et al., 1992). Compared to non-smokers, AMs from smokers appear to be in an 'active' state exhibiting increased microsomal and lysosomal enzymes, elevated resting rates of glucose utilization, increased production of oxygen radicals and myeloperoxidase activity, and increased migration and chemotactic responsiveness (reviewed in Sopori et al., 1994). However, in spite of this increased activity, AMs from smokers appear to be deficient in phagocytosis and/or bactericidal activity (Plowman, 1982).

Although cigarette smoking causes chronic pulmonary inflammation through macrophage accumulation in the alveoli and respiratory bronchioli, in general, their ability to produce/secrete biologically active substances is reduced. Thus, in response to LPS, AMs from smokers secreted lower levels of pro-inflammatory cytokines IL-1 and IL-6 and TNF-α (Brown et al., 1989; McCrea et al., 1994).

There is increasing evidence that cigarette smoking increases the risk of HIV infection and the development of AIDS. Epidemiological data indicate that among homosexual men, smokers are more likely than non-smokers to become HIV-1 seropositive (Burns et al., 1991). Moreover, the progression of HIV-1-seropositive individuals to develop AIDS or *P. carinii* infection is much faster in smokers than non-smokers (Nieman et al., 1993; Hirschtick et al., 1995). In addition, among HIV-1 positive women, the relative risk of HIV-1 transmission to their offspring is 3.3 times higher in smoking than non-smoking mothers (Burns et al., 1994). Furthermore, alveolar macrophages from HIV-1-infected smokers produce significantly more virus than non-smokers (Abbud et al., 1995). These obser-

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vations suggest that tobacco smoking may be a compounding factor in HIV-1 infection abetting the mechanisms involved in progression towards full-blown AIDS.

3. Effects of cigarette smoke on the immune system: animal studies

As in human studies, immunologic changes associated with cigarette smoke exposure are modified by several factors including the level and duration of exposure to cigarette smoke, tar and nicotine content of the smoke, and the species of the animal tested. Most of the animal studies have used rodents, especially rats and mice. There are inherent drawbacks in most rodent studies, because it is impractical to precisely replicate the characteristics patterns of human smoking. Thus, unlike humans, who smoke a given quantity of cigarettes over a period of about 16 h, animals are usually administered the daily dose of cigarette smoke in one or two sessions lasting only minutes. This would significantly reduce the exposure time of animals to the components of cigarette smoke which have relatively a short half-life. Nevertheless, animal experiments have provided useful results about the mechanism of cigarette smoke on the immune system.

Exposure of animals to cigarette smoke has been shown to lead to the inhibition of the primary antibody response (Holt and Keast, 1977; Sopori et al., 1985, 1989), less pronounced and/or short-lived splenomegaly and reduced expansion of splenic white pulp (Ayer et al., 1981), progressive decrease in resistance to transplanted tumors and increased tumor metastases and mortality (Thomas et al., 1974b; Chalmer et al., 1975). Cigarette smoke-induced changes in the antibody response may be biphasic i.e., acute exposures enhance while chronic exposures decrease the response (Thomas et al., 1973a, 1974a). Similar results were observed when the proliferative response to the T cell mitogen, PHA, was assessed in smoke-exposed animals (Thomas et al., 1973b). Moreover, cigarette smoke containing higher levels of tar and nicotine induced immunologic changes faster than smoke containing lower levels of tar and nicotine (Holt et al., 1976).

Chronic exposure of animals to cigarette smoke is also associated with increased susceptibility to infectious agents such as murine sarcoma virus (Thomas et al., 1974b) and influenza virus (Mackenzie, 1976). Similarly, clearance of *Pseudomonas aeruginosa* and antibody titer against *Micropolyspora faeni* in the lung was significantly decreased in smoke-exposed animals (Holt and Keast, 1977). Antibody response to both T cell-dependent and T cell-independent antigens may be impaired in chronically smoke exposed animals (Sopori et al., 1989; Goud et al., 1992). While chronic exposures to cigarette smoke may inhibit the primary antibody response, smoking does not appear to significantly affect the secondary antibody response (Thomas et al., 1973a). Thus, the immune system of smokers may function normally when responding to an antigen or pathogen encountered prior to smoking.

4. Components of cigarette smoke that may affect the immune response

The observation that exposure to smoke from high-tar high-nicotine cigarettes is more immunosuppressive than the smoke from low-tar low-nicotine cigarettes (Holt et al., 1976), suggests that tar and nicotine may be important immunotoxic components within cigarette smoke. Most of the tar, nicotine, and genotoxicity of cigarette smoke is associated with the particulate phase of cigarette smoke (Hoffmann et al., 1979; Hoffmann and Wynder, 1986). Chronic exposure of rats to the vapor phase of cigarette smoke does not lead to significant changes in the immune response, indicating that immunosuppressive properties of cigarette smoke are mainly associated with the particulate phase of cigarette smoke (Sopori et al., 1993). The particulate phase of cigarette smoke contains thousands of different compounds including most of the nicotine, polycyclic aromatic hydrocarbons (PAHs), tobacco glycoprotein (TGP), and some metals (US Department of Health and Human Services, 1993). There is increasing evidence that chronic nicotine treatment leads to inhibition of the antibody response indicating that nicotine is a major immunosuppressive component in cigarette smoke (Geng et al., 1995, 1996). Polycyclic aromatic hydrocarbons (PAHs) such as benzo[a]pyrene and benzo[a]anthracene are known immunosuppressants (reviewed in White et al., 1994). On the other hand, TGP and metals present in cigarette smoke are generally immunostimulatory (Francus et al., 1992; Brooks et al., 1990). Moreover, acute and chronic administration of PAHs such a benzo[a]pyrene may stimulate (Schnizlein et al., 1982) or inhibit (White, 1986) the immune response. Thus, effects of cigarette smoke on the immune system may reflect the cumulative effects of both immunosuppressive and immunostimulatory components of cigarette smoke. In addition, these effects may depend on the dose and duration of exposure.

5. Mechanism(s) of cigarette smoke-induced changes in the immune system

From the above discussion, it is clear that chronic exposures to cigarette smoke suppress the antibody response, and nicotine may significantly contribute to this immunosuppression. Xenobiotics have been shown to affect immunoregulation by several mechanisms and cigarette smoke/nicotine could potentially affect the immune system by the following mechanisms.

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5.1. Neuroimmune modulation and cigarette smoke

The mammalian immune system consists of an integrated network of various cell types, and a xenobiotic or its metabolite may regulate the immune function indirectly by affecting other organ systems, which may subsequently modulate immune function. There is an intimate relationship between the neuroendocrine and the immune systems during the development, maturation, and aging processes. Thus, the immune and neuroendocrine systems communicate bidirectionally through sharing of signal molecules such as cytokines, hormones, and neurotransmitters acting on receptors common to both systems (Blalock, 1994).

Nicotine is absorbed quickly through the pulmonary capillary blood flow. It readily crosses the blood brain barrier and is a classical sympathoadrenal stimulant (Braubar, 1995). Nicotine has been shown to produce a dose-dependent increase in cerebral glucose uptake, indicating increased brain metabolic activity (London et al., 1985a). Moreover, there are high affinity nicotine-binding sites in the hypothalamus (London et al., 1985b) and nicotine stimulates the expression of *c-fos* protein in the parvocellular paraventricular nucleus and brainstem catecholaminergic regions (Matta et al., 1993). While there may be several ways through which the immune system communicates with the nervous system, one of the well-defined pathways is via the hypothalamic–pituitary–adrenal (HPA) axis (reviewed in Fuchs and Sanders, 1994). Nicotine is a potent stimulator of the HPA axis resulting in the rapid secretion of ACTH (Seyler et al., 1984, 1986). Cigarette smoke and nicotine increase the concentrations of norepinephrine and epinephrine in plasma (Cryer et al., 1976; Pomerleau et al., 1983; Seyler et al., 1986; Van Loon et al., 1987). Both ACTH and catecholamines have been shown to inhibit the immune response (Fuchs and Sanders, 1994). In fact, the immunosuppressive effects of organophosphates have also been attributed to cholinergic stimulation (Casale et al., 1983). Thus, the HPA axis potentially contributes to cigarette smoke/nicotine-induced immunosuppression.

5.2. Cytokines and cigarette smoke

Cells of the immune system communicate with each other via cell–cell interactions and production of cytokines, and these molecules exert their biological effects through specific receptors expressed on the target cell membrane. In general, cytokines affect many types of cells and tissues exerting a wide range of biological effects (Kishimoto et al., 1994). Moreover, several cytokines may affect the same target cell type to mediate similar functions. For example, antibody production of B cells is induced by IL-2, IL-4, IL-5, IL-6, IFNγ, and several other cytokines.

Based on cytokine production profiles, $CD4^+$ T helper cells (Th) are divided into three major subtypes: Th1, characterized by production of IL-2 and IFN-γ; Th2, producing IL-4, IL-5, and IL-10; and Th0, which are not restricted in their lymphokine production (Mosmann and Coffman, 1989; Fearon and Locksley, 1996). Divergence of Th0 into Th1 and Th2 cell types is regulated by cytokines from other cells at the onset of infection through production of IL-12, IL-4, and IL-10 (Hsieh et al., 1993; Pearce and Reiner, 1995; Sher and Ahmed, 1995; Trinchieri, 1995; Fearon and Locksley, 1996). Among immune cells, macrophages produce IL-4 and are clearly the major producers of IL-12 and IL-10 (Gordon et al., 1995; Trinchieri, 1995). While IL-12 stimulates the conversion of Th0 cells to Th1 cells, IL-10 and IL-4 tend to convert them into Th2 type cells (Manetti et al., 1993; Seder et al., 1993; Fearon and Locksley, 1996). Moreover, IL-12 may actively curtail the production of IL-4 from Th2 cells (Manetti et al., 1993; Trinchieri, 1995). It has also been demonstrated that Th1 and Th2 cells down-regulate each other by their cytokines, IFN-γ and IL-4, respectively (Pearce and Reiner, 1995; Trinchieri, 1995). In addition, cytokines may affect the overall composition of classes/subclasses of antibodies produced (e.g., IL-4 stimulates murine B cells to produce IgE and IgG1 [IgG4 in humans]), whereas IFNγ induces mouse B cells to produce IgG2a (in humans IgG1) (Fearon and Locksley, 1996). Cigarette smokers have significantly higher levels of serum IgE (Burrows et al., 1981; Bahna et al., 1983) and, compared to non-smokers, peripheral blood mononuclear cells from cigarette smokers produce much higher levels of IL-4 (Byron et al., 1994). Thus, cigarette smoke may affect immune responses by altering the Th1/Th2 ratio. In fact, cigarette smoke-associated airway hyperreactivity is believed to be a Th2-driven disorder, and neutralization of IL-4 with monoclonal antibodies has been shown to markedly decrease serum IgE levels and the airway hyperreactivity (Kuhn et al., 1991; McCrea et al., 1994; Drazen et al., 1996).

Quality and quantity of cytokines made during an infection may markedly affect the resistance/susceptibility to a pathogen. For example, IFN-γ-producing Th1 cells are required for the immunity against *Listeria monocytogens*. Similarly, resistance to *Leishmania major* is associated with Th1-dominated responses (Kaufmann, 1995; Pearce and Reiner, 1995). Furthermore, reduction in the expression of IL-12 receptors may lead to loss of the Th1 response and increased susceptibility to some intracellular pathogens even under low IL-4 levels (Guler et al., 1996; Nobe-Trauth et al., 1996). Viruses such as HIV-1 have been shown to decrease Th1/Th2 ratios and this switch towards higher numbers of Th2 cells may be critical in the development of AIDS (Clerici et al., 1993). Therefore, Th1/Th2 ratios can have a significant impact on the type of cytokines produced and the outcome of an infection. In fact, many parasites induce high levels of IgE, which is believed to blunt the Th1-type cell responses (Marrack and Kappler, 1994). Through such mechanisms, cigarette

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smoking may, therefore, facilitate the effects of HIV-1 infection on the immune system by influencing the Th1/Th2 ratio.

Another manner through which cigarette smoke may affect the immune response is through modulation of the pro-inflammatory cytokines IL-1, IL-6, and TNF-α. These cytokines are known to play an important role in the immune response to infections (Balkwill, 1993; Marrack and Kappler, 1994). Compared to non-smokers, alveolar macrophages from smokers secrete significantly less IL-1, IL-6, and TNF-α (Brown et al., 1989; Yamaguchi et al., 1989; Soliman and Twigg, 1992; McCrea et al., 1994; Sauty et al., 1994). Nicotine treatment is also associated with inhibition of IL-1 and TNF-α production from colonic mucosa (Van Dijk et al., 1995). These observations may account for the increased susceptibility of smokers to infections but a decreased incidence of some autoimmune/inflammatory diseases such as ulcerative colitis, Farmer's lung, and sarcoidosis (Sopori et al., 1994). Although whole cigarette smoke and nicotine appear to inhibit pro-inflammatory cytokines, some components of cigarette smoke, such as TGP are known to stimulate the production of these cytokines (Francus et al., 1992).

5.3. Effects of cigarette smoke/nicotine on cell signaling

The biochemical events in the activation of lymphocytes, following stimulation with an antigen or mitogen, are under intense investigation. We and others have observed that chronic exposures to cigarette smoke/nicotine impairs the proliferative response of T cell antigens and mitogens (Sopori et al., 1994; Geng et al., 1995). Lymphocytes are activated by cross-linking of receptors by ligands leading to proliferation and differentiation of these cells (Cambier et al., 1994; Weiss and Littman, 1994). The failure of T lymphocytes from cigarette smoke/nicotine-treated animals to respond to TCR-mediated stimulations indicates that these T cells fail to transduce signals originating from the plasma membrane following the binding of ligand to antigen receptors. One of the earliest events in the receptor-mediated activation of cells is an increase in the intracellular Ca^{2+} levels ($[Ca^{2+}]_i$) (Clapham, 1995). T cells from rats chronically treated with cigarette smoke or nicotine exhibit a significantly lower rise in $[Ca^{2+}]_i$ in response to cross-linking of T cell receptor (TCR) with antibodies to TCR/CD3 complex (Sopori et al., 1993; Geng et al., 1995). Therefore, at least one of the lesions potentially contributing to immunosuppression is proximal to the antigen-induced Ca^{2+} response in T cells. To evaluate how cigarette smoke/nicotine may affect the antigen-induced signaling cascade in T lymphocytes, a simplified version covering the major steps in this pathway is presented below.

Signaling through TCR can lead to profound biological responses including activation, tolerance, and/or differentiation depending on the nature of the stimulus and the differentiation state of the lymphocytes (Chan et al., 1994). Following the ligation of TCR, one of the first observed events is the activation of protein tyrosine kinases (PTKs) and phospholipase Cγ1 (PLCγ1) activities (Chan et al., 1994). Tyrosine-containing motifs are found in multiple copies in the invariant chains of the TCR/CD3 complex, and following ligation of TCR, src-like kinases phosphorylate at these tyrosine-containing motifs creating docking sites for the binding of PLCγ1 (Berridge, 1993). Two families of PTKs have been implicated in T cell receptor signaling. Mutations either in the src-family kinase, Lck, or the syk-family kinase, ZAP-70 block activation through TCR (Chan et al., 1994). The activated (tyrosinephosphorylated) PLCγ1 binds the plasma membrane where it hydrolyzes phosphatidylinositol 4,5-bisphosphate (PIP2) into diacylglycerol (DAG) and inositol 1,4,5-trisphosphate (IP3) (Berridge, 1993; Weiss and Littman, 1994). IP3 stimulates the release of Ca^{2+} from IP3-sensitive Ca^{2+} stores in the endoplasmic reticulum (ER), leading to a rise in $[Ca^{2+}]_i$. Intracellularly, ER is the largest of the Ca^{2+} stores (Clapham, 1995), and it has been recently demonstrated that these Ca^{2+} stores are critical for transport of molecules between cytoplasm and nucleus (Greber and Gerace, 1995).

The condition in which antigen-specific T cells fail to respond to an antigen is called T cell anergy (T cell tolerance). Animals chronically exposed to cigarette smoke or nicotine do not exhibit significant changes in the number or distribution of T cell subsets (Savage et al., 1991; Geng et al., 1995), however, these cells fail to respond normally to stimulations with antigens or mitogens (Geng et al., 1995), indicating that T cells are non-responsive (anergic/tolerant) (Geng et al., 1996). Recently, it has been demonstrated that tolerance in antigen-specific T cell clones may develop as a result of partial T cell activation. For example, T cell anergy associated with stimulation of T cell clones with altered antigens, has been attributed to abnormal stimulation and failure to activate ZAP-70 (Sloan-Lancaster et al., 1994; Madrenas et al., 1995). Similarly, tolerant T cell clones were found to have lower $[Ca^{2+}]_i$ in response to antigen, in spite of activated PTKs activity and higher intracellular levels of IP3 (Gajewski et al., 1994). Thus, critical changes in PTK activity or the Ca^{2+} response may lead to T cell anergy through defective T cell activation. Xenobiotics that alter these responses could potentially cause T cell anergy. We have recently observed that the deceased ability of T cells from nicotine-treated rats to mobilize intra[A-cellular calcium in response to ligation of the antigen-receptor is associated with arrest of these cells in the G1 phase of the cell cycle (Geng et al., 1995). However, these cells had higher levels of IP3 and exhibited tyrosine phosphorylation of several substrates including PLCγ1 (Geng et al., 1996). These results suggest that chronic nicotine causes 'partial activation' of T cells. Partial activation of antigen-specific T cell clones results in T cell anergy (Gajewski et al., 1994;

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Sloan-Lancaster et al., 1994; Madrenas et al., 1995) and 7,12-dimethylbenz[a]anthracene-induced immunosuppression may be related to PTK activation (Archuleta et al., 1993). These observations suggest that PTK activation may be a generalized mechanism by which xenobiotics induce T cell tolerance and immunosuppression.

6. Conclusion

Based on available scientific evidence, chronic exposure to mainstream and sidestream tobacco smoke appears to impair the immune system in man and experimental animals. In addition, both mainstream and sidestream tobacco smoke may cause airway hyperreactivity. Cigarette smoke is a complex mixture of thousands of different chemical compounds and, depending on the dose and time period of exposure, some of these may cause immunostimulation or immunosuppression (Sopori et al., 1994). Recent evidence suggest that nicotine, one of the major components of cigarette smoke, inhibits the immune system (Geng et al., 1995).

The mechanism of cigarette smoke-induced immunosuppression is poorly understood; however, based on the known effects of cigarette smoke on various biological functions, several potential mechanisms could be operative (Fig. 1). Cigarette smoke as well as nicotine stimulate the release of catecholamines and ACTH (Cryer et al., 1976; Seyler et al., 1984, 1986) which have been associated with depressed immunity (Fuchs and Sanders, 1994). Interestingly, there is an inverse relationship between AIDS severity and plasma ACTH levels (Catania et al., 1993). Thus, cigarette smoke and HIV-infection may cooperate in inducing immunodeficiency and enhancing the development of AIDS through neuroimmune mechanisms.

Another mechanism by which cigarette smoke could potentially affect the immune response is by altering Th1/Th2 ratios. Leukocytes from smokers have the ability to produce higher levels of IL-4, a Th2 cytokine which stimulates IgE production and inhibits the Th1 cells required for the inflammatory response. Invading organisms, including HIV-1 and Epstein–Barr virus target and blunt pro-inflammatory cytokines by decreasing the Th1/Th2 ratio (Clerici et al., 1993; Marrack and Kappler, 1994). Similarly, many parasites induce high levels of IgE and it is postulated that IgE synthesis inhibits Th1 and inflammation (Marrack and Kappler, 1994). Cigarette smoke/nicotine increase IgE levels and inhibit pro-inflammatory cytokines (Bahna et al., 1983; McCrea et al., 1994; Sauty et al., 1994). Thus, cigarette smoke/nicotine may facilitate infection by various pathogens including HIV by blunting pro-inflammatory cytokines.

Although cigarette smoke appears to affect functions of both B and T cells (Sopori et al., 1994), there is increasing evidence that chronic treatment with cigarette smoke/nicotine induces functional unresponsiveness

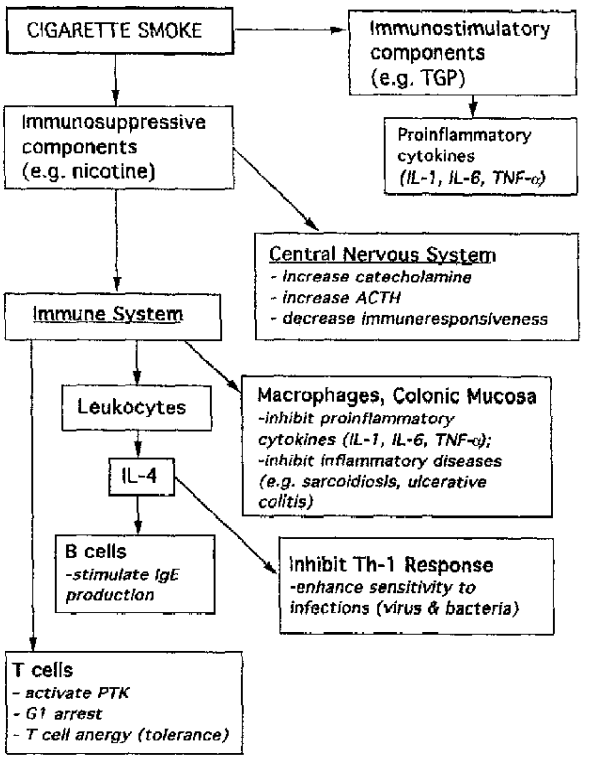

Fig. 1. An over-simplified model by which cigarette smoke could affect the immune system.

(anergy) in T cells. Studies from our laboratory (Geng et al., 1995, 1996) indicate that nicotine-induced T cell anergy may arise through its effects on the antigen-mediated signal transduction pathway leading to 'partial activation' and arrest of T cells in the G1 phase of the cell cycle. Recent results from our laboratory indicate that T cells from chronically nicotine-treated animals have depleted IP3-sensitive Ca^{2+} pools in ER. These Ca^{2+} pools have been recently shown to be critical in the active transport of molecules between the cytoplasm and the nucleus (Greber and Gerace, 1995). As yet, the molecular mechanism of T cell anergy is not fully clear; the ability of nicotine to induce T cell unresponsiveness may provide an excellent in vivo model to study this phenomenon.

The ability of smokers to resist infections including HIV-1 may be adversely affected, because exposure to cigarette smoke can lead to T cell anergy. Although smokers infected with HIV-1 have elevated numbers of $CD4^+$ T cells compared to HIV-infected non-smokers (Park et al., 1992), a significant proportion of these cells may represent the functionally inert (anergic) T cell population. Thus, in spite of higher CD4 T cells, the functional incompetence of these cells in HIV-infected smokers may accelerate the course of AIDS. While some laboratories have failed to observe significant effects of cigarette smoking on the development of AIDS (Craib et al., 1996), others report

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that HIV-infected smokers have significantly higher incidence of bacterial pneumonia than HIV-infected non-smokers with similar numbers of CD4 T cells (Burns et al., 1991; Nieman et al., 1993; Hirschtick et al., 1995), suggesting a lower efficiency of T cells in smokers to resist infections.

It is becoming clear that while cigarette smoking increases the risk of cancer and heart disease, it also limits the risk of several diseases. Cigarette smokers have a lower incidence of ulcerative colitis, sarcoidosis, pigeon breeder's disease, farmer's lung, environmental allergies (Sopori et al., 1994), and acne (Mills et al., 1993). We believe most of these beneficial effects may be associated with the anti-inflammatory effects of nicotine in inhibiting pro-inflammatory cytokines. Preliminary results from our laboratory show that nicotine-treated mice resist lethal infections of influenza virus better than untreated mice. Nicotine may also improve some cognitive functions in senescence and Alzheimer's disease (Meguro et al., 1994; Arendash et al., 1995; James and Nordberg, 1995; Wilson et al., 1995). Understanding the cellular and molecular mechanisms through which cigarette smoke/nicotine affects these responses may prove very useful in elucidating the underlying causes thereby leading to the development of treatments for many important human diseases.

Acknowledgements

This work was supported in part by grants from the National Institute of Drug Abuse DA04208 and DA05662. We thank Dr. M.I. Luster (National Institute for Occupational Safety and Health, Morgantown, WV) for his helpful suggestions about the manuscript.

References

Abbud, R.A., Finegan, C.K., Guay, L.A., Rich, E.A., 1995. Enhanced production of human immunodeficiency virus type-1 by in vitro infected alveolar macrophages from otherwise healthy cigarette smokers. J. Infec. Dis. 172, 859–863.

Adesina, A.M., Vallyathan, V., McQuillen, Weaver, S.O., Craighead, J.E., 1991. Bronchiolar inflammation and fibrosis associated with smoking. Am. Rev. Respir. Dis. 143, 144–149.

Andersen, P., Pedersen, D.F., Bach, B., Bonde, G.J., 1982. Serum immunoglobulins in smokers and non-smokers. Clin. Exp. Immunol. 47, 467–473.

Archuleta, M.M., Schieven, G.L., Ledbetter, J.A., Deanin, G.G., Burchiel, S.W., 1993. 7,12-dimethylbenz[a]anthracene activates protein–tyrosine kinases Fyn and Lck in the HPB-ALL human T-cell line and increases tyrosine phosphorylation of phospholipase C-γ1, formation of inositol 1,4,5-trisphosphate, and mobilization of intracellular calcium. Proc. Natl. Acad. Sci. U.S.A. 90, 6105–6109.

Arendash, G.W., Sengstock, G.J., Sandberg, R.R., Kem, W.R., 1995. Improved learning and memory in aged rats with chronic administration of nicotinic receptor agonist GTS-21. Brain Res. 674, 242–259.

Aronson, M., Weiss, S., Ben, R., Komaroff, A., 1982. Association between cigarette smoking and acute respiratory tract illness in young adults. JAMA 248, 181–183.

Ayer, D.J., Keast, D., Papadimitriou, J.M., 1981. Effects of tobacco smoke on splenic architecture and weight, during the primary immune response of BALB/c mice. J. Pathol. 133, 53–59.

Bahna, S.L., Heiner, D.C., Myhre, B.A., 1983. Immunoglobulin E pattern in cigarette smokers. J. Allergy Clin. Immunol. 38, 57–64.

Balkwill, F., 1993. Cytokines in health and disease. Immunol. Today 14, 149–150.

Berridge, M.J., 1993. Inositol trisphosphate and calcium signaling. Nature 361, 315–325.

Blalock, J.E., 1994. The immune system, our sixth sense. Immunologist 2, 8–15.

Bosken, C.H., Hards, J., Gatter, K., Hogg, J.C., 1992. Characterization of the inflammatory reaction in the peripheral airways of cigarette smokers using immunocytochemistry. Am. Rev. Respir. Dis. 145, 911–917.

Braubar, N., 1995. Direct effects of nicotine on the brain, evidence for chemical addiction. Arch. Environ. Health 50, 263–266.

Brooks, S.M., Baker, D.B., Gann, P.H., Jarabek, A.M., Hertzberg, V., Gallagher, J., Biagini, R.E., Bernstein, I.L., 1990. Cold air challenge and platinum skin reactivity in platinum refinery workers. Chest 97, 1401–1407.

Brown, G.P., Iwamoto, G.K., Monick, M.M., Hunninghake, G.W., 1989. Cigarette smoking decreases interleukin-1 release by human alveolar macrophages. Am. J. Physiol. 256, C260–C264.

Burns, D.N., Kramer, A., Yellin, F., Fuchs, D., Wachter, H., DiGiora, R.A., Sanchez, W.C., Grossman, R.J., Gordin, F.M., Biggar, R.J., 1991. Cigarette smoking, a modifier of human immunodeficiency virus type 1 infection?. J. AIDS 4, 76–83.

Burns, D.N., Landesman, S., Muenz, L.R., Nugent, R.P., Goedert, J.J., Minkoff, H., Walsh, J.H., Mendez, H., Rubinstein, A., Willoughby, A., 1994. Cigarette smoking, premature rupture of membranes, and vertical transmission of HIV-1 among women with low $CD4^+$ levels. J. AIDS 7, 718–726.

Burrows, B., Lebowitz, M.D., Barbee, R.A., 1976. Respiratory disorders and allergy skin test reactions. Ann. Int. Med. 84, 134–139.

Burrows, B., Halonen, M., Barbee, R.A., Lebowitz, M.D., 1981. The relationship of serum immunoglobulin E to cigarette smoking. Am. Rev. Respir. Dis. 124, 523–525.

Burrows, B., Halonen, M., Lebowitz, M.D., Knudson, R.J., Barbee, R.A., 1982. The relationship of serum immunoglobulin E, allergy skin test, and smoking to respiratory disorders. J. Allergy Clin. Immunol. 70, 199–204.

Byron, K.A., Varigos, G.A., Wootton, A.M., 1994. IL-4 production is increased in cigarette smokers. Clin. Exp. Immunol. 95, 333–336.

Cambier, J.C., Pleiman, C.M., Clark, M.R., 1994. Signal transduction by the B cell antigen receptor and its co-receptors. Ann. Rev. Immunol. 12, 457–486.

Casale, G.P., Cohen, S.D., DiCapua, R.A., 1983. The effects of organophosphate-induced cholinergic stimulation on the antibody response to sheep erythrocytes in inbred mice. Toxicol. Appl. Pharmacol. 68, 198–205.

Catania, A., Airaghi, L., Manfredi, M.G., Vivirito, M.C., Milazzo, F., Lipton, J.M., Zanussi, C., 1993. Proopiomelanocortin-derived peptides and cytokines, relations in patients with acquired immunodeficiency syndrome. Clin. Immunol. Immunopathol. 66, 73–79.

Chalmer, J., Holt, P.G., Keast, D., 1975. Cell-mediated immune response to transplanted tumors in mice chronically exposed to fresh cigarette smoke. J. Natl. Cancer Inst. 52, 1129–1134.

Chan, A., Desai, D., Weiss, A., 1994. The role of tyrosine kinases and protein tyrosine phosphatases in the antigen receptor signal transduction. Ann. Rev. Immunol. 12, 555–592.

Clapham, D.E., 1995. Calcium signaling. Cell 80, 258–268.

Clerici, M., Hakim, F.T., Venzon, D.J., Blatt, S., Hendrix, C.W., Wynn, T.A., Shearer, G.M., 1993. Changes in interleukin-2 and interleukin-4 produced in asymptomatic, human immunodeficiency virus-seropositive individuals. J. Clin. Invest. 91, 759–765.

PM3006731058

Source: https://www.industrydocuments.ucsf.edu/docs/xlvj0001

Corre, F., Lellouch, J., Schwartz, D., 1971. Smoking and leukocyte counts. Results of an epidemiological survey. Lancet 2, 632–634.

Craib, K.J.P., Schechter, M.T., Montaner, J.S., Le, T.N., Sestak, P., Willoughby, B., Voigt, R., Haley, L., O'Shaughnessy, M.V., 1996. The effects of cigarette smoking on lymphocyte subsets and progression to AIDS in a cohort of homosexual men. Clin. Invest. Med. 15, 301–308.

Cryer, P.E., Hymond, M.W., Santiago, J.V., Shah, S.D., 1976. Norepinephrine and epinephrine release and adrenergic mediation of smoking-associated hemodynamic and metabolic events. N. Engl. J. Med. 295, 573–577.

Doll, R., Peto, R., 1976. Mortality in relation to smoking, 20 years observation on male British doctors. Br. Med. J. 2, 1525–1535.

Drazen, J.M., Arm, J.P., Austen, K.F., 1996. Sorting out the cytokines of asthma. J. Exp. Med. 183, 1–5.

Dube, M.F., Green, C.R., 1982. Methods of collection of smoke for analytical purposes. Recent Adv. Tobacco Sci. 8, 42–102.

Fearon, D.T., Locksley, R.M., 1996. Instructive role of innate immunity in the acquired immune response. Science 272, 50–54.

Ferson, M., Edwards, A., Lind, A., Milton, G.W., Hershy, P., 1979. Low natural killer-cell activity and immunoglobulin levels associated with smoking human subjects. Int. J. Cancer 23, 603–609.

Finklea, J., Sandifer, S., Smith, D., 1969. Cigarette smoking and epidemic influenza. Am. J. Epidemiol. 90, 390–399.

Francus, T., Romano, P.M., Manzo, G., Fonacier, L., Arango, N., Szabo, P., 1992. IL-1, IL-6, and PDGF mRNA expression in alveolar cells following stimulation with tobacco-derived antigen. Cell. Immunol. 145, 156–174.

Fuchs, B.A., Sanders, V.M., 1994. The role of brain-immune interaction in immunotoxicology. Crit. Rev. Toxicol. 24, 151–176.

Gajewski, T.F., Qian, D., Fields, P., Fitch, F.W., 1994. Anergic T-lymphocyte clones have altered inositol phosphate, calcium, and tyrosine kinase signaling pathways. Proc. Natl. Acad. Sci. U.S.A. 91, 38–42.

Geng, Y., Savage, S.M., Johnson, L.J., Seagrave, J., Sopori, M.L., 1995. Effects of nicotine on the immune response: I. Chronic exposure to nicotine impairs antigen receptor-mediated signal transduction in lymphocytes. Toxicol. Appl. Pharmacol. 135, 268–278.

Geng, Y., Savage, S.M., Razani-Boroujerdi, S., Sopori, M.L., 1996. Effects of nicotine on the immune response: II. Chronic nicotine treatment induces T cell anergy. J. Immunol. 156, 2384–2390.

Gerrard, J.W., Heiner, D.C., Ko, C.G., Mink, J., Meyers, A., Dosman, J.A., 1980. Immunoglobulin levels in smokers and non-smokers. Ann. Allergy 44, 261–262.

Gordon, S., Clarke, S., Greaves, D., Doyle, A., 1995. Molecular immunobiology of macrophages, recent progress. Curr. Opin. Immunobiol. 7, 24–33.

Goud, S.N., Kaplan, A.M., Subbarao, B., 1992. Effects of cigarette smoke on the antibody response to thymic independent antigens from different lymphoid tissues of mice. Arch. Toxicol. 66, 164–169.

Greber, U., Gerace, L., 1995. Depletion of calcium from the lumen of endoplasmic reticulum reversibly inhibits passive diffusion and signal-mediated transport into the nucleus. J. Cell Biol. 128, 5–14.

Guler, M.L., Gorham, J.D., Hsieh, C.-S., Mackey, A.J., Steen, R.J., Dietrich, W.F., Murphy, K.M., 1996. Genetic susceptibility to Leishmania: IL-12 responsiveness in TH1 cell development. Science 271, 984–987.

Haynes, W.F.J., Krstulovic, V.J., Bell, A.J., 1966. Smoking habit and incidence of respiratory tract infections in a group of adolescent males. Am. Rev. Respir. Dis. 93, 780–785.

Hirschtick, R.E., Glassroth, J., Jordan, M.C., Wilcosky, T.C., Wallace, J.M., Kvale, P.A., Markowitz, N., Rosen, M.J., Mangura, B.T., Hopewell, P.C., 1995. Bacterial pneumonia in persons infected with the human immunodeficiency virus. Pulmonary complication of HIV infection study group. N. Engl. J. Med. 333, 845–851.

Hoffmann, D., Wynder, E.L., 1986. Chemical constituents and bioactivity of tobacco smoke. IARC Sci. Publ. 74, 145–165.

Hoffmann, D., Rivenson, A., Hecht, S.S., Hilfrich, I., Kobayashi, N., Wynder, E.L., 1979. Model studies in tobacco carcinogenesis with Syrian golden hamster. Prog. Exp. Tumor Res. 24, 370–390.

Holt, P.G., 1987. Immune and inflammatory function in cigarette smokers. Thorax 42, 241–249.

Holt, P.G., Keast, D., 1977. Environmentally induced changes in immunological function, acute and chronic effects of inhalation of tobacco smoke and other atmospheric contaminants in man and experimental animals. Bacteriol. Rev. 41, 205–216.

Holt, P.G., Chalmer, J., Roberts, L.M., Papadimitriou, J.M., Thomas, W.R., Keast, D., 1976. Low-tar high-tar cigarettes, comparison of effects in mice. Arch. Environ. Health 31, 258–265.

Hsieh, C.-S., Macatonia, S.E., Tripp, C.S., Wolf, S.F., O'Garra, A., Murphy, K.M., 1993. Development of Th1 $CD4^+$ T cells through IL-12 produced by Listeria-induced macrophages. Science 260, 547–549.

Hughes, D.A., Haslam, P.L., Townsend, P.J., Turner-Warwick, M., 1985. Numerical and functional alteration in circulatory lymphocytes in cigarette smokers. Clin. Exp. Immunol. 61, 459–466.

James, J.R., Nordberg, A., 1995. Genetic and environmental aspects of the role of nicotinic receptors in neurodegenerative disorders, emphasis on Alzheimer's disease. Behav. Genetics 25, 149–159.

Johnson, J.D., Hauchens, D.P., Kluwe, W.M., Craig, D.K., Fisher, G.L., 1990. Effects of mainstream and environmental tobacco smoke on the immune system in animals and humans, a review. Crit. Rev. Toxicol. 20, 369–395.

Kark, J., Lebiush, M., Rannon, L., 1982. Cigarette smoke as a risk factor for epidemic A (H^1N^1) influenza in young men. N. Engl. J. Med. 307, 1042–1046.

Kaufmann, S.H.E., 1995. Immunity to intracellular microbial pathogens. Immunol. Today 16, 338–342.

Kishimoto, T., Taga, T., Akira, S., 1994. Cytokine signal transduction. Cell 76, 253–262.

Kuhn, R., Rajewsky, K., Muller, W., 1991. Generation and analysis of interleukin-4 deficient mice. Science 254, 707–710.

London, E.D., Connolly, R.J., Szikszay, M., Wamsley, J.K., 1985a. Distribution of cerebral metabolic effects of nicotine in the rat. Eur. J. Pharmacol. 110, 391–392.

London, E.D., Waller, S.B., Wamsley, J.K., 1985b. Autoradiographic localization of [^{3}H]-nicotine binding sites in the rat brain. Neurosci. Lett. 53, 179–184.

Mackenzie, J.S., 1976. The effects of cigarette smoke on influenza virus, a murine model system. Life Sci. 19, 409–412.

Madrenas, J., Wange, R.L., Wang, J.L., Isakov, N., Samelson, L.E., Germain, R.N., 1995. ζ phosphorylation without ZAP-70 activation induced by TCR antagonists or partial agonists. Science 267, 515–518.

Manetti, R., Parronchi, P., Giudizi, M.G., Piccinni, M.P., Maggi, E., Trinchieri, G., Romagnani, S., 1993. Natural killer cell stimulatory factor (interleukin-12 [IL-12]) induces T helper type 1 (Th1)-specific immune responses and inhibits development of IL-4 producing cells. J. Exp. Med. 177, 1199–1204.

Marrack, P., Kappler, J., 1994. Subversion of immune system by pathogens. Cell 76, 323–332.

Matta, S.G., Foster, C.A., Sharp, B.M., 1993. Nicotine stimulates the expression of c-*fos* protein in the parvocellular paraventricular nucleus and brainstem catecholaminergic regions. Endocrinology 132, 2149–2156.

McCrea, K.A., EnSor, J.E., Nall, K., Bleecker, E.R., Hasday, J.D., 1994. *Altered cytokine regulation in the lungs of cigarette smokers.* Am. J. Respir. Crit. Care Med. 150, 696–703.

Meguro, K., Yamaguchi, S., Arai, H., Nagagawa, T., Maruyama, Y., Sasaki, H., 1994. Nicotine improves cognitive disturbance in senescence-accelerated mice. Pharmacol. Biochem. Behav. 49, 769–772.

PM3006731059

Source: https://www.industrydocuments.ucsf.edu/docs/xlvj0001

Mills, C.M., Hill, S.A., Marks, R., 1993. Altered inflammatory responses in smokers. Br. Med. J. 307, 911.

Mosmann, T.R., Coffman, R.L., 1989. TH1 and TH2 cells, different patterns of lymphokine secretion lead to different functional properties. Ann. Rev. Immunol. 7, 145–173.

Nieman, R.B., Fleming, J., Cocker, R.J., Harris, J.R., Mitchell, D.M., 1993. The effect of cigarette smoking on the development of AIDS in HIV-1 seropositive individuals. AIDS 7, 705–710.

Nobe-Trauth, N., Kropf, P., Muller, I., 1996. Susceptibility to *Leishmania major* infection in interleukin-4-deficient mice. Science 271, 987–990.

Park, L.P., Margolick, J.B., Giorgi, J.V., Ferbs, J., Bauer, K., Kaslow, R., Munoz, A., 1992. Influence of HIV-1 infection and cigarette smoking on leukocyte profiles in homosexual men. The multi-center AIDS cohort study. J. AIDS 5, 1124–1130.

Pearce, E.J., Reiner, S.L., 1995. Induction of Th2 responses in infectious diseases. Curr. Opin. Immunol. 7, 497–504.

Plowman, P.N., 1982. The pulmonary macrophage population of human smokers. Am. Rev. Respir. Dis. 25, 393–405.

Pomerleau, O.F., Festing, J.B., Seyler, L.E., Jaffe, J., 1983. Neuroendocrine reactivity to nicotine in smokers. Psychopharmacology 81, 61–67.

Sauty, A., Mauel, J., Philippeaux, M.-M., Leuenberger, P., 1994. Cytostatic activity of alveolar macrophages from smokers and non-smokers. Role of interleukin-1β, interleukin-6, and tumor necrosis factor-α. Am. J. Respir. Cell Mol. Biol. 11, 631–637.

Savage, S.M., Donaldson, L.A., Cherian, S., Chilukuri, R., White, V.A., Sopori, M.L., 1991. Effects of cigarette smoke on the immune response: II. chronic exposure to cigarette smoke inhibits surface immunoglobulin-mediated responses in B cells. Toxicol. Appl. Pharmacol. 111, 523–529.

Schnizlein, C.T., Bice, D.E., Mitchell, C.E., Hahn, F.F., 1982. Effects on rat lung immunity by acute lung exposure to benzo[a]pyrene. Arch. Environ. Health 37, 201–206.

Seder, R.A., Gazzinelli, R.T., Sher, A., Paul, W.E., 1993. IL-12 acts directly on CD4$^+$ T cells to enhance priming for IFN-γ production and diminishes IL-4 inhibition of such priming. Proc. Natl. Acad. Sci. U.S.A. 90, 10188–10192.

Seyler, L.E. Jr., Fertig, J.B., Pomerleau, O.F., Hunt, D., Parker, K., 1984. The effects of smoking on ACTH and cortisol secretion. Life Sci. 34, 57–65.

Seyler, L.E. Jr., Pomerleau, O.F., Fertig, J.B., Hunt, D., Parker, K., 1986. Pituitary hormone response to cigarette smoking. Pharmacol. Biochem. Behav. 24, 159–162.

Sher, A., Ahmed, R., 1995. Immunity to infection. Curr. Opin. Immunol. 7, 471–473.

Sloan-Lancaster, J., Shaw, A.S., Rothbard, J.B., Allen, P.M., 1994. Partial T cell signaling, altered phospho-ξ and lack of ZAP-70 recruitment in APL-induced T cell anergy. Cell 79, 913–922.

Smart, Y.C., Cox, J., Roberts, T.K., Brinsmead, M.W., Burton, R.C., 1986. Differential effects of cigarette smoke on recruiting T lymphocyte subsets in pregnant women. J. Immunol. 137, 1–3.

Soliman, D.M., Twigg, H.L. III, 1992. Cigarette smoke decreases bioactive interleukin-6 secretion by alveolar macrophages. Am. J. Physiol. 263, L471–L478.

Sopori, M.L., Gairola, C.G., DeLucia, A.J., Bryant, L.R., Cherian, S., 1985. Immune responsiveness of monkeys exposed chronically to cigarette smoke. Clin. Immunol. Immunopathol. 36, 338–344.

Sopori, M.L., Cherian, S., Chilukuri, R., Shopp, G.M., 1989. Cigarette smoke causes inhibition of the immune response to intratracheally administered antigens. Toxicol. Appl. Pharmacol. 97, 489–499.

Sopori, M.L., Savage, S.M., Christner, R.F., Geng, Y., Donaldson, L.A., 1993. Cigarette smoke and the immune response: mechanism of nicotine-induced immunosuppression. Adv. Biosci. 86, 663–672.

Sopori, M.L., Goud, N.S., Kaplan, A.M., 1994. Effects of tobacco smoke on the immune system. In: Dean, J.H., Luster, M.I., Munson, A.E., Kimber, I. (Eds.), Immunotoxicology and Immunopharmacology, Raven Press, New York, pp. 413–434.

Stedman, R.L., 1968. The chemical composition of tobacco and tobacco smoke. Chem. Rev. 68, 153–207.

Thomas, W.R., Holt, P.G., Keast, D., 1973a. Effects of cigarette smoking on primary and secondary humoral responses in mice. Nature 243, 240–241.

Thomas, W.R., Holt, P.G., Keast, D., 1973b. Cellular immunity in mice chronically exposed to fresh cigarette smoke. Arch. Environ. Health 27, 372–375.

Thomas, W.R., Holt, P.G., Keast, D., 1974a. The development of alteration in the primary immune response of mice by exposure to fresh cigarette smoke. Int. Arch. Allergy Appl. Immunol. 46, 481–486.

Thomas, W.R., Holt, P.G., Papadimitriou, J.M., Keast, D., 1974b. The growth of transplanted tumors in mice after chronic inhalation of fresh cigarette smoke. Br. J. Cancer 30, 459–462.

Tollerud, D.J., Clark, J.W., Brown, L.M., Neuland, C.Y., Mann, D.L., Pankiw-Trost, L.K., Blattner, W.A., Hoover, R.N., 1989. Association of cigarette smoking with decreased numbers of circulating natural killer cells. Am. Rev. Respir. Dis. 139, 194–198.

Tollerud, D.J., Brown, L.M., Blattner, W.A., Mann, D.L., Pankiw-Trost, L., Hoover, R.N., 1991. T cell subsets in healthy black smokers and non-smokers. Evidence for ethnic group as an important response modifier. Am. Rev. Respir. Dis. 144, 612–616.

Trinchieri, G., 1995. Interleukin-12, a pro-inflammatory cytokine with immunoregulatory functions that bridge innate resistance and antigen-specific adaptive immunity. Ann. Rev. Immunol. 13, 251–276.

US Department of Health and Human Services, 1993. Respiratory health effects of passive smoking, lung cancer and other disorders, NIH Publication No. 93-3605, monograph 4.

US Department of Health and Human Services, 1994. CDC Morbidity and Mortality Weekly Report, Vol. 43, pp. 469–472.

US Department of Health, Education, and Welfare, 1979. A report of the Surgeon General: smoking and health, US Government Printing Office.

Van Dijk, J.P., Madretsma, G.S., Keuskamp, Z.J., Zijlstra, F.J., 1995. Nicotine inhibits cytokine synthesis by mouse colonic mucosa. Eur. J. Pharmacol. 278, R11–R12.

Van Loon, G.R., Kiritsy-Roy, J.A., Brown, L.V., Bobbitt, F.A., 1987. Nicotinic regulation of sympathoadrenal catecholamine secretion, cross tolerance to stress. In: Martin, W.R., Van Loon, G.R., Iwamato, E.T., Davis, L. (Eds.), Tobacco Smoking and Nicotine, A Neurobiological Approach, Plenum, New York, pp. 263–276.

Weiss, A., Littman, D.R., 1994. Signal transduction by lymphocyte antigen receptors. Cell 76, 263–274.

White, K.L. Jr., 1986. An overview of immunotoxicology and carcinogenic polycyclic aromatic hydrocarbons. J. Environ. Sci. Health C4, 163–202.

White, K.L. Jr., Kawabata, T.T., Ladics, G.S., 1994. Mechanism of polycyclic aromatic hydrocarbon immunotoxicity. In: Dean, J.H., Luster, M.I., Munson, A.E., Kimber I. (Eds.), Immunotoxicology and Immunopharmacology, Raven Press, New York, pp. 123–142.

Wick, G., Schett, G., Amberger, A., Kleindienst, R., Xu, Q., 1995. Is atherosclerosis an immunologically mediated disease?. Immunol. Today 16, 27–33.

Wilson, A.L., Langley, L.K., Monley, J., Bauer, T., Rottunda, S., McFalla, E., Kovera, C., McCarten, J.R., 1995. Nicotine patches in Alzheimer's disease, pilot study on learning, memory, and safety. Pharmacol. Biochem. Behav. 51, 509–514.

Yamaguchi, E., Okazaki, N., Itoh, A., Abe, S., Kawakami, Y., Okuyama, H., 1989. Interleukin-1 production by alveolar macrophages decreased in smokers. Am. Rev. Respir. Dis. 140, 397–402.

PM3006731060

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